IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of | ) | |
| | ) | |
| JONATHAN S. STAMLER | ) | Group Art Unit: 1654 |
| | ) | |
| Patent Application No. 09/757,610 | ) | Examiner: R.R. Teller |
| | ) | |
| Filed: January 11, 2001 | ) | |
| | ) | |
| For: INHIBITING GS-FDH TO MODULATE NO BIOACTIVITY | ) | |

BRIEF ON APPEAL (In Triplicate)

Honorable Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the decision of the Examiner in the final action of August 12, 2003. A Notice of Appeal was filed on November 12, 2003.

REAL PARTY IN INTEREST

The real parties in interest are Duke University and Nitrox, L.L.C.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

Claims 1-20 were in the application as filed and were subjected to a restriction requirement. Claims 8-14 were in the elected group. Claims 1-7 and 15-20 were withdrawn

from consideration and canceled. Claims 9, 10 and 12 were amended in the response of 13 November 2002. Claims 8-14 have been finally rejected and the rejection of all of them is appealed. A copy of the appealed claims is set forth in the Appendix hereto.

STATUS OF AMENDMENTS

Claims 1-7 and 15-20 have been canceled. Claims 9, 10 and 12 have been amended; there was no objection to the amendments. There were no amendments after the final rejection of August 12, 2003.

SUMMARY OF THE INVENTION

Stamler et al. U.S. patent No. 6,057,367 is directed to treating mammals for infections or for conditions associated with pathologically proliferating mammalian cell growth (for example, cancers, restenosis, benign prostatic hypertrophy) by administration of a manipulator of nitrosative stress (an impetus for NO or $NO_2$ group attachment to proteins, nucleic acids or other biological molecules) to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically proliferating mammalian cells. It has been concluded in the course of making the invention herein that inhibition of the enzyme glutathione-dependent formaldehyde dehydrogenase (GS-FDH) found in the mammals and pathological bacteria and fungi, mediates the nitrosative stress of U.S. Patent No. 6,057,367. (See the application as filed at page 3, lines 15 and 16). The embodiment of invention involved in this appeal involves treating a patient afflicted with pathologically proliferating cells comprising administering a therapeutically effective amount of an inhibitor of GS-FDH and is described in these terms in the application as filed at page 3, lines

10-14. .The pathologically proliferating cells can be pathologic bacteria or fungal cells (see the application as filed at page 19, lines 16-20) or pathologically proliferating cancer cells or pathologically proliferating cells causing restenosis (see the application as filed at page 20, lines 10-18 and Examples XV-XXV in the application as filed at pages 40-42). Preferred treating agents include D-glutathione (see the application as filed at page 22, line 6).

ISSUE

Whether a rejection based on 35 U.S.C. 112, first paragraph, is proper when the specification teaches how to use, when there is a presumption of enablement in this case because of the issuance of U.S. Patent No. 6,057,367, when Dermer and Gura are not contested as being defective to negate enablement and when the Wands factors are otherwise improperly applied.

GROUPING OF THE CLAIMS

The rejected claims do not stand or fall together. As indicated in the Argument section, applicant has different positions on Claims 8, 10, 11 and 14 which embrace treating a mammalian patient afflicted with pathologically proliferating cancer cells (with no particular kinds of cancer being mentioned); Claim 12 which embraces treating mammalian patients where the pathologically proliferating cells are those in Hodgkins disease, in small cell lung cancer, in cancer of the breast, in testicular cancer or in prostate cancer and the treatment kills or reduces the rate of growth of the pathologically proliferating cells; Claim 13 which embraces treating a patient where the pathologically proliferating cells are those causing restenosis (a condition different from cancer); and Claim 10 where the pathologically proliferating cells comprise

pathologic bacteria or fungus and the treatment of an infected patient kills or reduces the rate of proliferation of the pathologic bacteria or fungus.

ARGUMENT

The Rejection

Claims 8-14 have been rejected under 35 U.S.C. 112, first paragraph on the basis that the specification while being enabling for administering an inhibitor of glutathione-dependent formaldehyde dehydrogenase does not reasonably provide enablement for killing or reducing the [rate of] growth of pathologically proliferating mammalian cells *in vivo*.

The final rejection makes contentions involving some of the Wands factors but ignores or incompletely applies others.

The main contention involves the quality of experimentation necessary. The final rejection takes the position that the working examples lack sufficient data in view of "teaching of unpredictability regarding *in vivo* therapy which taught in the prior art" (i.e., which is different from Dermer, Biotechnology 12, 320 (3/94) or Gura, Science 278, 1041-1042 (11/97).

In an office action dated May 19, 2003, reliance was placed on Dermer, Biotechnology 12, 320 (3/94) which takes the position that *in vitro* data on cancer is a poor representation as basis for *in vivo* treatment of cancer. The conclusion based on Dermer in the office action of May 19, 2003 is that the working examples do not contain sufficient data to understand if the results will invariably occur. The final rejection does not dispute applicant's position in the response of June 9, 2003, that Dermer is defective as a basis for this position.

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predictive for drugs for cancer in humans. The rejection was withdrawn after applicant's response to the Gura position. The office action of May 19, 2003 reinstates the rejection under 35 U.S.C. 112, first paragraph, "for reasons of record" and additionally for new reasons. But Gura is not mentioned and the implication is that it is not a basis for the reinstated rejection.

So far as the amount of direction or guidance provided, the office action of May 19, 2003 says that the specification is defective in failing to provide data allowing determination of "how to avoid the pitfalls in the process of using the therapy."

The rejection of May 19, 2003 does not discuss the working examples with any specificity.

So far as the nature of the invention is concerned, the rejection of May 19, 2003 describes it as relating to providing therapy for pathologically proliferating mammalian cells.

The rejection of May 19, 2003 describes the state of the prior art as being unpredictable when involved with cancer and pathologically proliferating mammalian cells. The rejection ignores U.S. Patent No. 6,057,367. Moreover, said description excludes Claim 9.

The relative skill in the art is described in the office action of May 19, 2003 as a practicing M.D. skilled in clinical research. No evidence is submitted to support this.

The rejection of May 19, 2003 states that the art indicates unpredictability so far as cancer therapies and therapies for pathologically proliferating mammalian cells. The statement excludes Claim 9.

So far as breadth of the claims is concerned, the rejection of May 19, 2003 says that the claims are directed to therapies for cancer and for pathologically proliferating mammalian cells. The statement excludes Claim 9 and overgeneralizes with respect to Claims 12 and 13.

The final rejection maintains these positions.

The Law

In general, enablement involves the legal determination of whether the patent application teaches how to make and use without undue experimentation being necessary.

One subset involves whether undue experimentation is necessary to determine how to use in relation to one of the steps of a method regardless of scope. This is the subset which facts in Mineral Separation v. Hyde and In re Wands and United States v. Techtronic, cited in the Advisory Action of 12/20/2000, are directed.

Another subset involves whether undue experimentation is needed over some portion of the scope of a claim. These kinds of rejections are known as scope of enablement rejections. For this subset, the burden is on the PTO to support by evidence or reasoning its doubts on enablement. See In re Dinh-Nguyen, 181 U.S.P.Q. 46 (CCPA 1974); In re Bowen, 181 U.S.P.Q. 48 (CCPA 1974); In Re Ambruster, 185 U.S.P.Q. 152 (CCPA 1975); and Ex parte Reese, 40 U.S.P.Q. 2nd 1221 (Bd. App. 1996).

The first described subset is the one here.

Compliance with 37 C.F.R. 1.92(c)(8)(i)(A)

37 C.F.R. 1.92(c)(8)(i)(A) requires a description of the subject matter of each rejected claim.

All the rejected claims (Claims 8-14) are directed to a method for treating a patient afflicted with pathologically proliferating cells. The method comprises administering to said patient a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase (GS-FDH). Claim 8 is the independent claim and is directed to the method as recited in this paragraph.

Claim 14 depends from Claim 8 and names the treating agent as D-glutathione.

Claims 9, 10, 11, 12 and 13 depend directly or indirectly from Claim 8 and are more specific than Claim 8 in naming kinds of pathologically proliferating cells.

Claim 10 depends from Claim 8 and names the pathologically proliferating cells as mammalian cells.

Claim 11 depends from Claim 8 and names the pathologically proliferating mammalian cells as being cancer cells and is the claim to which the evidence relied on in the office action of May 19, 2003 is most specifically directed.

Claim 12 depends from Claim 11 and names five kinds of cancers, namely Hodgkins disease, small cell lung cancer, cancer of the breast, testicular cancer and prostate cancer.

Claim 13 depends form Claim 10 and names the pathologically proliferating cells as those causing restenosis (not cancer).

Claim 9 depends fro Claim 1 and names the pathologically proliferating cells as comprising pathologic bacteria or fungus (i.e., not mammalian cells). The pathologic bacteria or fungus infect the patient. The administration of the invention treats the infection.

Compliance with 37 C.F.R. 1.92(c)(8)(i)(B)

Compliance with 37 C.F.R. 1.92(c)(8)(i)(B) requires indication of how the specification enables one skilled in the art to make and use the subject matter defined in each of the rejected claims. Since the rejected claims are method claims, the issue is how to use. Demonstration of how to use follows.

Treating agents are described in the application as filed at page 18, line 15 - page 19, line 4. Dosage is set forth in the application as filed at page 20, line 21 - page 21, line 5. Routes of administration are set forth in the application as filed at page 21, lines 7-22.

So far as disease states are concerned, "pathologically proliferating mammalian cells" are defined in the application as filed at page 20, lines 10-13. Five kinds of cancers are named in the application as filed at page 20, 16-18. Other diseases caused by or involving pathologically proliferating mammalian cells including restenosis are described in the application as filed at page 20, lines 13-16. So far as the invention of Claim 9 is concerned, pathologically proliferating microbes are described in the application as filed at page 16-20.

Prophetic working Examples XV-XXVI (pages 40-42 of the application as filed) give detail.

Compliance with 37 C.F.R. 1.92(c)(8)(i)(C)

Compliance with 37 C.F.R. 1.92(c)(8)(i)(C) requires an indication of how the application sets forth the best mode of carrying out the invention.

Best mode is indicated in prophetic working Examples XV-XXVI of the application as filed.

Best mode is not an issue in this appeal.

Compliance with Requirement in 37 C.F.R. 1.192(c)(8)(i)
that the Argument Shall Specify the Errors in the Rejection

There is an error firstly in the rejection of Claims 8-14 in that it fails to recognize that the only question involved in determining enablement in this case is whether the specification teaches how to use. For this case, In re Hitchings, 144 U.S.P.Q. 637 (CCPA 1965) indicates an express disclosure of manner of administration and dosage, will satisfy the how to use requirement. Dosage and route administration are clearly set forth at page 21 of the application

as filed and are exemplified in Examples XV-XXVI at pages 40-42 of the application as filed. Thus, the how to use requirement is clearly met. The office action of May 19, 2003 admits that the specification is enabling for administering an inhibitor of glutathione-dependent formaldehyde dehydrogenase. That is all that is required to meet the enable requirement here. The Wands factors are irrelevant here because the application is admittedly sufficient in respect to how to use.

Even if the Wands factor are pertinent, these is error secondly in respect to the rejection of Claims 8-14 because the office action fails to consider pertinent prior art, namely Stamler et al. U.S. Patent No. 6,057,367, which is presumptively enabled because it has issued and is directed to treating mammals for infections and with conditions associated with pathologically proliferating cell growth by administration of a manipulator of nitrosative stress (an impetus for NO or $NO_2$ group attachment to proteins, nucleic acid or other biological molecules) to selectively kill or reduce the growth of microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically proliferating mammalian cells. The invention of Claims 8-14 relies on the discovery that a known enzyme, namely GS-FDH, has S-nitrosoglutathione reductase activity and therefore would mediate the proliferation of pathologically proliferating cells by interfering with nitrosative stress and that inhibiting GS-FDH would therefore mediate the presence of nitrosative stress which is taught in U.S. Patent No. 6,057,367 to kill or reduce the growth of pathologically proliferating cells. See the application as filed at page 2, lines 15-16. That inhibiting GS-FDH mediates nitrosative stress is indicated at pages 33 and 34 of the application as filed and the widespread nature of GS-FDH/GSNO reductase activity in human cells and microbes is shown in Background Example I which starts at page 28 of the application as filed. Thus, there is presumptively enablement here

because of U.S. Patent No. 6,057,367 and the rejections have not rebutted the presumptive enablement.

There is error thirdly in respect to the rejection of Claims 8-14 because of the position in the rejection that the examples lack sufficient data to understand if the clinical results will invariably occur. No case law has been cited to support the "will invariably occur" standard and that cannot be the standard because almost no known medical treatment would meet that standard. Rarely is any medical treatment effective in all cases and even a 5% effective rate would be considered remarkable in the case of an otherwise fatal disease. The undersigned's wife has undergone treatment for severe rheumatoid arthritis costing $15,000 - $30,000 per month and that treatment did not work in the case of the undersigned's wife. Yet the treatments are FDA approved and apparently provide good results in some cases. To spare some of the consequences of severe rheumatoid arthritis is a remarkable event and for that reason the treatment is recognized as a operative treatment.

There is error fourthly because the rejection takes the position that there is no enablement because the working examples provided lack sufficient data to determine how to avoid the pitfalls in the process of using the therapy, but has failed to meet the required burden of proving there are pitfalls that need to be avoided in this case.

There is error fifthly because the final office action of August 12, 2003 gives up on Dermer and Gura to prove unpredictability after noting the contentions in applicant's responses of June 9, 2003 and November 13, 2002 and states "However, the Examiner notes that based on the teachings of unpredictability regarding *in vivo* therapy which are taught in the prior art, persons skilled in the art would not associate *in vitro* results with *in vivo* therapeutic therapy." This is a defective legal position. The office action does not say what "the prior art is" or supply

copies thereof. The position in the final office action is simply an *ipse dixit*. This is insufficient legally. Rather evidence is required. Consider the following excerpt from the recent decision by the Board of Patent Appeals and Interferences in 08/474,796:

> Instead of a fact-based reasoned analysis as to why appellant's disclosure does not provide an enabling description of the claimed invention, we find only the examiner's unsupported conclusion that the specification does not enable the claimed invention. In this regard, we note the examiner's numerous references to the "state of the art" (Answer, page 5); missing however, is a citation to any reference that provides a factual basis upon which to question the predictability of appellants' claimed invention. In this regard, we remind the examiner that findings of fact and conclusions of law by the USPTO must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706 (A),(E), 1994. Dickinson v. Zurko, 527 US 150, 158, 119 S. Ct. 1816, 1821, 50 USPQ2d 1930, 1934 (1999). Our review court has held that finding of fact must be supported by substantial evidence within the record. In re Gartside,, 203 F. 3d 1305, 1315, 53 USPQ3d 1769, 1775 (Fed. Cir. 2000)

Claim 9

Claim 9 additionally avoids the rejection because there never has been any evidence asserted which related to the case where the pathologically proliferating cells are pathologically proliferating bacteria or fungi. The final office action seems to contend without basis that evidence with respect to unpredictability on cancer should count in respect to bacteria and fungi.

Claim 13 additionally avoids the rejection because there never has been any evidence asserted that there is unpredictability with respect to pathologically proliferating mammalian cells that are not cancer cells.

Claim 12 additionally avoids the rejection because it names five kinds of cancers and prophetic working Examples XX, XIX, XXI, XXII and XXIII (pages 40-42 of the application as filed) are directed respectively to each of these kinds of cancer.

It is submitted that enablement has been shown.

REQUEST

Reversal of the rejection and allowance of Claims 8-14 is requested.

It is noted that there have been four office actions that are not restriction requirements. These office actions have not been prompted by any action on behalf of applicant except for applicant providing convincing contentions in opposition. In view of this, it is submitted that the only appropriate actions in response should be allowance or an Examiner's answer.

Respectfully submitted,

By: _____

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Date: January 30, 2004

## APPENDIX

## APPEALED CLAIMS

8. A method for treating a patient afflicted with pathologically proliferating cells, said method comprising administering to said patient a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase.

9. The method of Claim 8 where the pathologically proliferating cells comprise pathologic bacteria or fungus and the patient is afflicted with a bacterial or fungal infection which is mediated or caused by the pathologic bacteria or fungus and the administering kills the pathologic bacteria or fungus or reduces the rate of proliferation of the pathologic bacteria or fungus by at least 10%.

10. The method of Claim 8 where the pathologically proliferating cells are pathologically proliferating mammalian cells and the administering kills the pathologically proliferating mammalian cells or reduces the rate of proliferation of the pathologically proliferating cells by at least 10%.

11. The method of Claim 10 wherein the pathologically proliferating mammalian cells are cancer cells.

12. The method of Claim 11 wherein the pathologically proliferating mammalian cells are those in Hodgkin's disease, in small cell lung cancer, in cancer of the breast, in testicular cancer or in prostate cancer.

13. The method of Claim 10 wherein the pathologically proliferating cells are those causing restenosis.

14. The method of Claim 8 wherein the inhibitor is D-glutathione.

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## STATUS OF THE CLAIMS

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from consideration and canceled. Claims 9. 10 and 12 were amended in the response of 13 November 2002. Claims 8-14 have been finally rejected and the rejection of all of them is appealed. A copy of the appealed claims is set forth in the Appendix hereto.

## STATUS OF AMENDMENTS

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## SUMMARY OF THE INVENTION

Stamler et al. U.S. patent No. 6.057.367 is directed to treating mammals for infections or for conditions associated with pathologically proliferating mammalian cell growth (for example, cancers. restenosis, benign prostatic hypertrophy) by administration of a manipulator of nitrosative stress (an impetus for NO or $NO_2$ group attachment to proteins. nucleic acids or other biological molecules) to selectively kill or reduce the growth of the microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically proliferating mammalian cells. It has been concluded in the course of making the invention herein that inhibition of the enzyme glutathione-dependent formaldehyde dehydrogenase (GS-FDH) found in the mammals and pathological bacteria and fungi, mediates the nitrosative stress of U.S. Patent No. 6,057.367. (See the application as filed at page 3, lines 15 and 16). The embodiment of invention involved in this appeal involves treating a patient afflicted with pathologically proliferating cells comprising administering a therapeutically effective amount of an inhibitor of GS-FDH and is described in these terms in the application as filed at page 3, lines

10-14. The pathologically proliferating cells can be pathologic bacteria or fungal cells (see the application as filed at page 19, lines 16-20) or pathologically proliferating cancer cells or pathologically proliferating cells causing restenosis (see the application as filed at page 20, lines 10-18 and Examples XV-XXV in the application as filed at pages 40-42). Preferred treating agents include D-glutathione (see the application as filed at page 22, line 6).

ISSUE

Whether a rejection based on 35 U.S.C. 112, first paragraph, is proper when the specification teaches how to use, when there is a presumption of enablement in this case because of the issuance of U.S. Patent No. 6,057,367, when Dermer and Gura are not contested as being defective to negate enablement and when the Wands factors are otherwise improperly applied.

GROUPING OF THE CLAIMS

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pathologic bacteria or fungus and the treatment of an infected patient kills or reduces the rate of proliferation of the pathologic bacteria or fungus.

ARGUMENT

The Rejection

Claims 8-14 have been rejected under 35 U.S.C. 112, first paragraph on the basis that the specification while being enabling for administering an inhibitor of glutathione-dependent formaldehyde dehydrogenase does not reasonably provide enablement for killing or reducing the [rate of] growth of pathologically proliferating mammalian cells *in vivo*.

The final rejection makes contentions involving some of the Wands factors but ignores or incompletely applies others.

The main contention involves the quality of experimentation necessary. The final rejection takes the position that the working examples lack sufficient data in view of "teaching of unpredictability regarding *in vivo* therapy which taught in the prior art" (i.e., which is different from Dermer, Biotechnology 12, 320 (3/94) or Gura, Science 278, 1041-1042 (11/97).

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The relative skill in the art is described in the office action of May 19, 2003 as a practicing M.D. skilled in clinical research. No evidence is submitted to support this.

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The Law

In general, enablement involves the legal determination of whether the patent application teaches how to make and use without undue experimentation being necessary.

One subset involves whether undue experimentation is necessary to determine how to use in relation to one of the steps of a method regardless of scope. This is the subset which facts in Mineral Separation v. Hyde and In re Wands and United States v. Techtronic, cited in the Advisory Action of 12/20/2000, are directed.

Another subset involves whether undue experimentation is needed over some portion of the scope of a claim. These kinds of rejections are known as scope of enablement rejections. For this subset, the burden is on the PTO to support by evidence or reasoning its doubts on enablement. See In re Dinh-Nguyen, 181 U.S.P.Q. 46 (CCPA 1974); In re Bowen, 181 U.S.P.Q. 48 (CCPA 1974); In Re Ambruster, 185 U.S.P.Q. 152 (CCPA 1975); and Ex parte Reese, 40 U.S.P.Q. 2nd 1221 (Bd. App. 1996).

The first described subset is the one here.

Compliance with 37 C.F.R. 1.92(c)(8)(i)(A)

37 C.F.R. 1.92(c)(8)(i)(A) requires a description of the subject matter of each rejected claim.

All the rejected claims (Claims 8-14) are directed to a method for treating a patient afflicted with pathologically proliferating cells. The method comprises administering to said patient a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase (GS-FDH). Claim 8 is the independent claim and is directed to the method as recited in this paragraph.

Claim 14 depends from Claim 8 and names the treating agent as D-glutathione.

Claims 9. 10. 11. 12 and 13 depend directly or indirectly from Claim 8 and are more specific than Claim 8 in naming kinds of pathologically proliferating cells.

Claim 10 depends from Claim 8 and names the pathologically proliferating cells as mammalian cells.

Claim 11 depends from Claim 8 and names the pathologically proliferating mammalian cells as being cancer cells and is the claim to which the evidence relied on in the office action of May 19. 2003 is most specifically directed.

Claim 12 depends from Claim 11 and names five kinds of cancers. namely Hodgkins disease. small cell lung cancer. cancer of the breast. testicular cancer and prostate cancer.

Claim 13 depends form Claim 10 and names the pathologically proliferating cells as those causing restenosis (not cancer).

Claim 9 depends fro Claim 1 and names the pathologically proliferating cells as comprising pathologic bacteria or fungus (i.e.. not mammalian cells). The pathologic bacteria or fungus infect the patient. The administration of the invention treats the infection.

Compliance with 37 C.F.R. 1.92(c)(8)(i)(B)

Compliance with 37 C.F.R. 1.92(c)(8)(i)(B) requires indication of how the specification enables one skilled in the art to make and use the subject matter defined in each of the rejected claims. Since the rejected claims are method claims. the issue is how to use. Demonstration of how to use follows.

Treating agents are described in the application as filed at page 18, line 15 - page 19, line 4. Dosage is set forth in the application as filed at page 20, line 21 - page 21. line 5. Routes of administration are set forth in the application as filed at page 21, lines 7-22.

So far as disease states are concerned, "pathologically proliferating mammalian cells" are defined in the application as filed at page 20, lines 10-13. Five kinds of cancers are named in the application as filed at page 20, 16-18. Other diseases caused by or involving pathologically proliferating mammalian cells including restenosis are described in the application as filed at page 20, lines 13-16. So far as the invention of Claim 9 is concerned, pathologically proliferating microbes are described in the application as filed at page 16-20.

Prophetic working Examples XV-XXVI (pages 40-42 of the application as filed) give detail.

Compliance with 37 C.F.R. 1.92(c)(8)(i)(C)

Compliance with 37 C.F.R. 1.92(c)(8)(i)(C) requires an indication of how the application sets forth the best mode of carrying out the invention.

Best mode is indicated in prophetic working Examples XV-XXVI of the application as filed.

Best mode is not an issue in this appeal.

Compliance with Requirement in 37 C.F.R. 1.192(c)(8)(i)
that the Argument Shall Specify the Errors in the Rejection

There is an error firstly in the rejection of Claims 8-14 in that it fails to recognize that the only question involved in determining enablement in this case is whether the specification teaches how to use. For this case, In re Hitchings, 144 U.S.P.Q. 637 (CCPA 1965) indicates an express disclosure of manner of administration and dosage, will satisfy the how to use requirement. Dosage and route administration are clearly set forth at page 21 of the application

as filed and are exemplified in Examples XV-XXVI at pages 40-42 of the application as filed. Thus, the how to use requirement is clearly met. The office action of May 19, 2003 admits that the specification is enabling for administering an inhibitor of glutathione-dependent formaldehyde dehydrogenase. That is all that is required to meet the enable requirement here. The Wands factors are irrelevant here because the application is admittedly sufficient in respect to how to use.

Even if the Wands factor are pertinent, these is error secondly in respect to the rejection of Claims 8-14 because the office action fails to consider pertinent prior art, namely Stamler et al. U.S. Patent No. 6,057,367, which is presumptively enabled because it has issued and is directed to treating mammals for infections and with conditions associated with pathologically proliferating cell growth by administration of a manipulator of nitrosative stress (an impetus for NO or $NO_2$ group attachment to proteins, nucleic acid or other biological molecules) to selectively kill or reduce the growth of microbes or helminths causing the infection or of host cells infected with the microbes or of the pathologically proliferating mammalian cells. The invention of Claims 8-14 relies on the discovery that a known enzyme, namely GS-FDH, has S-nitrosoglutathione reductase activity and therefore would mediate the proliferation of pathologically proliferating cells by interfering with nitrosative stress and that inhibiting GS-FDH would therefore mediate the presence of nitrosative stress which is taught in U.S. Patent No. 6,057,367 to kill or reduce the growth of pathologically proliferating cells. See the application as filed at page 2, lines 15-16. That inhibiting GS-FDH mediates nitrosative stress is indicated at pages 33 and 34 of the application as filed and the widespread nature of GS-FDH/GSNO reductase activity in human cells and microbes is shown in Background Example I which starts at page 28 of the application as filed. Thus, there is presumptively enablement here

because of U.S. Patent No. 6,057,367 and the rejections have not rebutted the presumptive enablement.

There is error thirdly in respect to the rejection of Claims 8-14 because of the position in the rejection that the examples lack sufficient data to understand if the clinical results will invariably occur. No case law has been cited to support the "will invariably occur" standard and that cannot be the standard because almost no known medical treatment would meet that standard. Rarely is any medical treatment effective in all cases and even a 5% effective rate would be considered remarkable in the case of an otherwise fatal disease. The undersigned's wife has undergone treatment for severe rheumatoid arthritis costing $15,000 - $30,000 per month and that treatment did not work in the case of the undersigned's wife. Yet the treatments are FDA approved and apparently provide good results in some cases. To spare some of the consequences of severe rheumatoid arthritis is a remarkable event and for that reason the treatment is recognized as a operative treatment.

There is error fourthly because the rejection takes the position that there is no enablement because the working examples provided lack sufficient data to determine how to avoid the pitfalls in the process of using the therapy, but has failed to meet the required burden of proving there are pitfalls that need to be avoided in this case..

There is error fifthly because the final office action of August 12, 2003 gives up on Dermer and Gura to prove unpredictability after noting the contentions in applicant's responses of June 9, 2003 and November 13, 2002 and states "However, the Examiner notes that based on the teachings of unpredictability regarding *in vivo* therapy which are taught in the prior art, persons skilled in the art would not associate *in vitro* results with *in vivo* therapeutic therapy." This is a defective legal position. The office action does not say what "the prior art is" or supply

copies thereof. The position in the final office action is simply an *ipse dixit*. This is insufficient legally. Rather evidence is required. Consider the following excerpt from the recent decision by the Board of Patent Appeals and Interferences in 08/474,796:

> Instead of a fact-based reasoned analysis as to why appellant's disclosure does not provide an enabling description of the claimed invention, we find only the examiner's unsupported conclusion that the specification does not enable the claimed invention. In this regard, we note the examiner's numerous references to the "state of the art" (Answer, page 5); missing however, is a citation to any reference that provides a factual basis upon which to question the predictability of appellants' claimed invention. In this regard, we remind the examiner that findings of fact and conclusions of law by the USPTO must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706 (A),(E), 1994. Dickinson v. Zurko, 527 US 150, 158, 119 S. Ct. 1816, 1821, 50 USPQ2d 1930, 1934 (1999). Our review court has held that finding of fact must be supported by substantial evidence within the record. In re Gartside., 203 F. 3d 1305, 1315, 53 USPQ3d 1769, 1775 (Fed. Cir. 2000)

Claim 9

Claim 9 additionally avoids the rejection because there never has been any evidence asserted which related to the case where the pathologically proliferating cells are pathologically proliferating bacteria or fungi. The final office action seems to contend without basis that evidence with respect to unpredictability on cancer should count in respect to bacteria and fungi.

Claim 13 additionally avoids the rejection because there never has been any evidence asserted that there is unpredictability with respect to pathologically proliferating mammalian cells that are not cancer cells.

Claim 12 additionally avoids the rejection because it names five kinds of cancers and prophetic working Examples XX, XIX, XXI, XXII and XXIII (pages 40-42 of the application as filed) are directed respectively to each of these kinds of cancer.

It is submitted that enablement has been shown.

REQUEST

Reversal of the rejection and allowance of Claims 8-14 is requested.

It is noted that there have been four office actions that are not restriction requirements. These office actions have not been prompted by any action on behalf of applicant except for applicant providing convincing contentions in opposition. In view of this, it is submitted that the only appropriate actions in response should be allowance or an Examiner's answer.

Respectfully submitted.

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Date: January 30, 2004

## APPENDIX

## APPEALED CLAIMS

8. A method for treating a patient afflicted with pathologically proliferating cells, said method comprising administering to said patient a therapeutically effective amount of an inhibitor of glutathione-dependent formaldehyde dehydrogenase.

9. The method of Claim 8 where the pathologically proliferating cells comprise pathologic bacteria or fungus and the patient is afflicted with a bacterial or fungal infection which is mediated or caused by the pathologic bacteria or fungus and the administering kills the pathologic bacteria or fungus or reduces the rate of proliferation of the pathologic bacteria or fungus by at least 10%.

10. The method of Claim 8 where the pathologically proliferating cells are pathologically proliferating mammalian cells and the administering kills the pathologically proliferating mammalian cells or reduces the rate of proliferation of the pathologically proliferating cells by at least 10%.

11. The method of Claim 10 wherein the pathologically proliferating mammalian cells are cancer cells.

12. The method of Claim 11 wherein the pathologically proliferating mammalian cells are those in Hodgkin's disease, in small cell lung cancer, in cancer of the breast, in testicular cancer or in prostate cancer.

13. The method of Claim 10 wherein the pathologically proliferating cells are those causing restenosis.

14. The method of Claim 8 wherein the inhibitor is D-glutathione.